COVID-19 Vaccine Response in People Living with Sickle Cell Disease

PROTOCOL NO.:

ASH RC CTN 2021-00001
WCG IRB Protocol #20212379

PROTOCOL VERSION: 2.0
PROTOCOL DATE: 14Apr2022

SPONSOR: American Society of Hematology Research Collaborative

Study Principal Investigators:

Charles S. Abrams, MD
University of Pennsylvania

Sophie Lanzkron, MD
Johns Hopkins University

Participating Sites: TBD

Table of Contents

Study Summary

Title	COVID-19 Vaccine Response in People Living with Sickle Cell Disease
Short Title	COVID-19 Vaccine Response in Sickle Cell Disease
Study Population and Duration	Up to 200 subjects with sickle cell disease will be enrolled at up to 20 sites in the United States. Subjects will participate in the study for approximately 6 months.
Objectives	**Primary Objective:** to measure antibody response to COVID-19 vaccination in a cohort of persons with SCD. **Secondary Objective:** to assess for unexpected side effects of COVID-19 vaccination in a cohort of persons with SCD.
Main Inclusion and Exclusion Criteria	**Inclusion Criteria** 1. Diagnosis of sickle cell disease (HbSS, HbSC, $HbSB^0$ thalassemia, $HbSB^+$ thalassemia, HbS/Other) 2. Has not received any COVID vaccination prior to enrollment 3. Scheduled for a COVID vaccination (type does not matter) as part of routine care 4. Willing to sign consent **Exclusion Criteria** 1. Unwilling to have labs drawn or complete study requirements. 2. Previous therapy curative of SCD (including bone marrow transplant and gene therapy) 3. Previous receipt of anti-COVID-19 antibody therapy

1 Background and Study Rationale

Sickle cell disease (SCD) is a genetic disorder caused by a single base substitution of valine for a glutamine at the sixth amino acid of the gene encoding for the hemoglobin β chain. Patients with Hgb SS disease or other sickle hemoglobinopathies suffer from a variety of clinical complications related to this abnormal hemoglobin.

These clinical manifestations include hemolytic anemia and painful or vaso-occlusive crisis that occurs when sludging in the microcirculation causes tissue hypoxia. In addition to the painful events, SCD patients generally auto-splenectomize in childhood secondary to infarctions from their hemoglobinopathy[1], thus increasing their risk of infection and rendering them immunosuppressed.

Patients with SCD are considered at increased risk of complications from infection from SARS-CoV-2 infection and are therefore an important group to receive vaccination against the virus. In data published from a COIVD-19 registry, 69% of patients with SCD diagnosed with COVID-19 were hospitalized, 11% required ICU admission and 7% died.[2] The mean patient age was <40 years, raising significant concern about the risks associated with COVID-19 infection in individuals with SCD.

Data suggest that general immune function in SCD patients may be impaired, and thus responses to vaccine may be suboptimal. One example is the decreased efficacy of hepatitis B vaccination in children with SCD. Although this vaccine is highly effective in the general pediatric population, a clinical trial in children with SCD showed that only 89% of subjects achieved a protective antibody level of >= 10 mIU/mL as compared to 97% of controls (p=0.002). However, 93% of the children who did not achieve protective immunity after the standard series of 3 doses of vaccine did achieve a protective titer after receiving a 4th dose, suggesting that a successful outcome can be achieved with a modified vaccination schedule[3]. There are multiple abnormalities in adaptive immunity in SCD which may explain decreased vaccine efficacy. A recent study demonstrated that sickle cell patients have an increased number of CD4+CD28null cells as compared to age- and race-matched controls, and in vitro studies have demonstrated these cells release high levels of pro-inflammatory cytokines. Treatment with hydroxyurea was demonstrated to decrease this dysfunctional immune cell population.[4] In addition, SCD patients have been shown to have a skewing of T helper cells towards a Th2 phenotype and a reduction in the ratio of CD4 helper to CD8+ T suppressor cells, both of which may contribute to a mild state of immunosuppression in SCD patients.[5]

These differences in immune cell populations have been characterized in vitro, but there is little evidence in the literature as to how this may affect SCD patients' ability to respond to vaccine antigens as well as infectious diseases. Concerns have been raised about response to vaccination to influenza[6], and the effect of the use of hydroxyurea on the seroconversion post yellow fever vaccination in people with SCD.[7] Understanding response to COVID-19 vaccination in this high-risk group of patients can provide a more targeted approach to vaccination and an assessment of whether additional doses of vaccine will be required in order to achieve adequate protection.

2 Study Objectives

- **Primary Objective**: to measure antibody response to COVID-19 vaccination in a cohort of persons with SCD.

- **Secondary Objective**: to assess for unexpected side effects of COVID-19 vaccination in a cohort of persons with SCD.

3 Investigational Plan

The purpose of this project is to monitor the antibody response to vaccination in this immunosupressed population and assess for unexpected side effects from vaccination. Subjects with sickle cell disease who are eligible to receive their initialCOVID-19 vaccination will be recruited and asked to provide informed consent. Prior to receiving COVID-19 vaccination, subjects will visit the study site to complete questionnaires and provide a blood sample. Following vaccination, subjects will be contacted by phone, text, or email to complete a survey (2 to 3 total). Subjects will return to the study site 2 and 6 months after vaccination to complete questionnaires and provide a blood sample. Blood samples will be analyzed for antibody response to the COVID-19 vaccine.

3.1 Study Endpoints

- **Primary endpoint:** IgG ELISA titer geometric mean at 2 months (56 days) after the initial vaccination.

- **Secondary endpoints:**

    - IgG ELISA titer geometric mean at 6 months after initial vaccination.

    - Side effects of vaccination and sickle cell related consequences of those side effects, as assessed by patient report and through validated survey instruments including ASCQ-Me, the Brief COPE scale and the Brief Pain Inventory for participants 18+ years of age, and PROMIS Pain Interference, and PROMIS Mobility for pediatric participants.

    - Incidence of patient reported COVID-19 infections in the 6-months following immunization with the COVID-19 vaccine.

4 Study Population and Duration of Participation

Up to 200 subjects will be enrolled at up to 20 sites in the United States. Subjects will participate in the study for approximately 6 months.

4.1 Inclusion Criteria

1. Diagnosis of sickle cell disease (HbSS, HbSC, $HbSB^0$ thalassemia, $HbSB^+$ thalassemia, HbS/Other)
2. Has not received any COVID-19 vaccination prior to enrollment
3. Scheduled for a COVID-19 vaccination (type does not matter) as part of routine clinical care*
4. Willing and able to sign consent

4.2 Exclusion Criteria

1. Unwilling to have labs drawn or complete study requirements.
2. Previous therapy curative of SCD (including bone marrow transplant and gene therapy)
3. Previous receipt of anti-COVID-19 antibody therapy

** Note: Inclusion Criteria #3 should be interpreted as the subject having made the decision to get vaccinated and having identified when and where they will be vaccinated. A subject's confirmation of their intent to get vaccinated, and the approximate date of their vaccination is sufficient to meet this inclusion criteria. This may be documented in the subject's medical records or the study source documentation after discussion with the subject.*

4.3 Subject Recruitment

Subjects will be recruited by study site physicians or their delegate. Information about the study may be shared with patients by their caring physician or through patient advocacy groups. Patients may be contacted by IRB approved letter, email, or phone call.

4.4 Vulnerable Populations:

This study will enroll participants under the age of 18 years. Subjects 12 to 17 years of age will be asked to review the consent form and provide assent. A parent or legal guardian must provide informed consent for subjects under 18 years of age to participate.

5 Study Procedures

5.1 Informed Consent

This study will allow either written documentation of informed consent and assent or verbal consent and assent depending on the site preference and local requirements.

Written Informed Consent

Participants will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation. This consent form will be reviewed and approved by the IRB for the study.

Before initiating any study procedures, study personnel will review the study in detail and the subject will have the opportunity to have questions answered. At the end of the consent discussion, the subjects will be asked to sign the consent form and return it to the study team. The same study personnel, in the capacity of "persons obtaining consent" will sign the consent form of the subject after the consent conversation occurs. Consent conversations will be documented. A signed copy of the consent will be provided to the subject. Informed consent may occur prior to Visit 1.

For subjects under the age of 18, a parent or legal guardian will provide permission using the consent procedures described above. In addition, subjects 12 – 17 years of age will be asked to review the consent form and provide assent.

Verbal Informed Consent

As this is a minimal risk study with procedures for which written consent would not normally be required outside of the research setting, verbal consent is sufficient for enrollment into this study.

Subjects will be provided with a "Consent Information Sheet" describing this study and providing sufficient information for subjects to make an informed decision about their participation. This document will be reviewed and approved by the IRB for the study. Before initiating any study procedures, study personnel will review the study in detail and the subjects will have the opportunity to have questions answered.

When possible, recruitment and consent discussions will occur on separate days to allow subjects interested in participating time to review the participant information document prior to being asked to provide consent. Participants that would like to enroll remotely will have a scheduled phone or video call with the study personnel during which the consent discussion will take place. Consent discussions will be led by trained study personnel guided by the content of the Consent Information Sheet.

Consent discussions will be documented, signed, and dated by the study personnel obtaining informed consent in the 'Record of Verbal Consent' document. A participant will be considered enrolled after they have provided verbal consent and received a copy of the participant information document, and the rest of the study procedures may commence.

For subjects under the age of 18, a parent or legal guardian will provide permission using the verbal consent procedures described above. In addition, subjects 12 – 17 years of age will be asked to review the Consent Information Sheet and provide assent.

5.2 Medical Record Review

Variables to be abstracted from medical charts (paper or electronic) include elements that fall under the below categories, as available through routine clinical practice or obtained as part of this study:

- Contact information and socio-demographics
- Diagnoses
- Biometrics
- Physical exam
- Vital signs
- Pathology
- Laboratory results
- Clinical features
- Co-morbid conditions
- Medications (previous and current)
- Treatments, procedures, and surgeries
- End of study information (including information on early withdrawal)

5.3 Questionnaires

Subjects will be asked to complete several questionnaires, either standard surveys used routinely in clinical practice or as approved by the IRB. These questionnaires include:

- COVID-19 Community Response Survey: Comorbidities and Care Engagement, Coronavirus Impact and Pandemic Stress; Other COVID-19 Questions
- Participants 18-years of age and older:
    - Adult Sickle Cell Questionnaire-Me (ASCQ-Me) Measures
        - Emotional impact
        - Pain impact
        - Social functioning
        - Stiffness impact

        - Sleep impact
    - Brief COPE Scale[8]
    - Brief Pain Inventory (BPI)
- Participants under 18 years of age:
    - PROMIS Pain Interference (8-17 years, or parent proxy)
        - Emotional Impact
        - Social Impact
        - Physical/Activity Impact
    - PROMIS Mobility (8-17 years, or parent proxy)
        - Impact on activities of physical mobility
- Additional surveys to assess health

5.4 Blood Draw

Up to 5ml of peripheral blood will be drawn at Visits 1, 5, and 6 to be tested for SARS-CoV2-specific antibody by enzyme-linked immunosorbent assay (ELISA). All biologic specimens will be shipped in a de-identified manner to Dr. Scott Hensley's lab at the University of Pennsylvania for analysis of antibodies.[10] All biospecimens will be destroyed at the completion of the study.

5.5 Schedule of Events

A table detailing the schedule of events is included in Appendix A.

5.5.1 Visit 1

Visit 1 will occur up to 30 days prior to the subject's first or only COVID-19 vaccination. This visit may occur on the same day as vaccination, as long as study procedures are completed prior to vaccination. Some of the procedures may occur remotely as long as the participant provides consent prior to any research procedures commencing. The following procedures will be performed at Visit 1:

- Informed consent (if not previously completed)
- Medical record review and intake history
- Demographics
- Questionnaires:
    - COVID-19 Community Response Survey: Comorbidities and Care Engagement, Coronavirus Impact and Pandemic Stress; Other COVID-19 Questions

  Participants 18-years of age and older:
    - Adult Sickle Cell Questionnaire-Me (ASCQ-Me) Measures
        - Emotional impact
        - Pain impact
        - Social functioning
        - Stiffness impact
        - Sleep impact
    - Brief COPE Scale
    - Brief Pain Inventory (BPI)

  Participants under 18 years of age:
    - PROMIS Pain Interference (8-17 years, or parent proxy for participants <8)
        - Emotional Impact
        - Social Impact
        - Physical/Activity Impact
    - PROMIS Mobility (8-17 years, or parent proxy for participants <8)

        - Impact on activities of physical mobility

- Blood drawn for assessment of antibodies

Participants who enroll but do not receive the first vaccination within 30 days of consent should proceed in the study and the out of window vaccination should be documented as a protocol deviation. Future visits are benchmarked to the date of the first vaccination.

5.5.2 Visit 2

Visit 2 will occur 2-3 days following the first COVID-19 vaccination (or only vaccination if receiving a single dose vaccine. The subject will be contacted by phone, email, or text to complete a survey including information about the vaccine type received, side effects, and sickle cell disease related symptoms.

5.5.3 Visit 3

Visit 3 will occur 14 days (±3 days) following the subject's first (only) COVID-19 vaccination. The subject will be contacted by phone, email, or text to complete a survey including information about side effects, and sickle cell disease related symptoms.

5.5.4 Visit 4

Visit 4 will occur 2-3 days following the second COVID-19 vaccination. If the subject received a single-dose vaccine, then Visit 4 will not occur. The subject will be contacted by phone, email, or text to complete a survey including information about the vaccine type received, side effects, and sickle cell disease related symptoms.

5.5.5 Visit 5

Visit 5 will occur 2 months (±1 week) following the subject's first (or only) COVID-19 vaccination. If a subject received a two-dose vaccine and the receipt of the second dose is administered more than 5 weeks after administration of the 1st dose, then the Visit 5 should also be delayed to occur 3 to 4 weeks after the second vaccination. If the second vaccination does not occur by the initial Visit 5 window, Visit 5 should occur as scheduled and the missed/delayed 2nd dose documented.

The following procedures will be performed at Visit 5:

- Questionnaires:
  Participants 18-years of age and older:
    - Adult Sickle Cell Questionnaire-Me (ASCQ-Me) Measures
        - Emotional impact
        - Pain impact
        - Social functioning
        - Stiffness impact
        - Sleep impact
    - Brief COPE Scale
    - Brief Pain Inventory (BPI)

  Participants under 18 years of age:
    - PROMIS Pain Interference (8-17 years, or parent proxy for participants <8 years)
        - Emotional Impact
        - Social Impact

        - Physical/Activity Impact
    - PROMIS Mobility (8-17 years, or parent proxy for participants <8 years)
        - Impact on activities of physical mobility
    - Kids Coping Scale[9] (7-17 years)

- Blood drawn for assessment of antibodies
- Collection of information regarding COVID-19 diagnosis, sickle cell disease complications, and COVID-19 vaccine administration.

5.5.6 Visit 6

Visit 6 will occur 6 months (±2 weeks) following the subject's first (or only) COVID-19 vaccination. The following procedures will be performed at Visit 6:

- Questionnaires
  Participants 18-years of age and older:
    - Adult Sickle Cell Questionnaire-Me (ASCQ-Me) Measures
        - Emotional impact
        - Pain impact
        - Social functioning
        - Stiffness impact
        - Sleep impact
    - Brief COPE Scale
    - Brief Pain Inventory (BPI)

  Participants under 18 years of age:
    - PROMIS Pain Interference (8-17 years or parent proxy for participants <8 years)
        - Emotional Impact
        - Social Impact
        - Physical/Activity Impact
    - PROMIS Mobility (8-17 years or parent proxy for participants <8 years)
        - Impact on activities of physical mobility
    - Kids Coping Scale[9] (7-17 years)
- Blood drawn for assessment of antibodies
- Collection of information regarding COVID-19 diagnosis, sickle cell disease complications, and COVID 19 vaccine administration.

If a vaccine booster dose is planned during the Visit 6 window, the blood draw for assessment of antibody titers should be collected prior to administration of the booster dose whenever possible.

5.5.7 Unscheduled Visits

An unscheduled visit may occur if needed to obtain an additional blood sample as a result of a lab error, poor specimen collection, etc.

5.6 Subject Withdrawal and Early Termination

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules. The Investigator may also withdraw subjects to protect the subject for reasons related to safety or for administrative reasons. It will be

documented whether or not each subject completes the study. Subjects who withdraw early will be asked to have one final visit to collect final evaluations.

6 Statistical Plan

Statistical considerations were based on the available data for serum IgG ELISA titers for the Moderna vaccine administered at 50 ug mRNA-1293 at 56 days post initial vaccination (28 days post vaccination 2 for those patients receiving a product requiring two vaccinations). Data were obtained from Table 10 in the VRBPAC briefing document provided to the FDA dated 12/17/2020 (page 29).[11] Per that document, the average log10 titer was 5.750 with a standard deviation of 0.2765.

It is assumed that 200 individuals with sickle cell disease will receive an available vaccine. The vaccine product administered will be recorded and all products will be pooled for use for analyses; power calculations are based on a total of 200 participants. It is anticipated that 60% of participants will be of SS or Sbeta0thal genotype and 40% will be SC or Sbeta+thal or less common genotypes. The primary goal is to provide estimates of geometric mean titer at 2 months following initial vaccination with a 95% confidence interval. The geometric mean approach will be used to address asymmetry in the distribution of titers. Under these assumptions there will be more than 99% power to detect a drop to a geometric mean titer (GMT) to 5.50, assuming a two-sided 0.05 significance level and the reported standard deviation. This high level of power will be retained for the 120 SS or SBeta0thal patients and the 80 SC or SBeta+thal patients separately. Should the standard deviation for sickle cell patients be three times that reported for healthy controls in Table 10 of the briefing document, at least 90% power will still be retained for each of the genotypic subsets.

It is not yet known whether an immune response to vaccination might trigger vaso-occlusive crises or other consequences of sickle cell disease. Side effects reported in vaccinated participants will be described, with an estimate of rate with a confidence interval. Such events might enhance any vaccine hesitancy that may already exist in this population, leading some participants to decline the second vaccination if they receive an mRNA vaccine. Therefore, the rate at which patients receive only one dose of mRNA vaccine will be assessed. These participants will be retained in the study and titers will be measured at 2 and 6 months.

It is acknowledged that vaccines against other diseases established fold change in titer from pre to post vaccination, with established fold change criteria for protection. Such guidelines are not available for COVID-19, and therefore the titers will be examined at the specified time points. At this time there is data to suggest that vaccination leads to exceedingly high antibody titers, but there is no data to suggest clinical consequences for subjects whose titers increase substantially but are less than exceedingly high.

7 Safety and Adverse Events

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms

- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Only adverse events with Grade 2 or higher per Common Terminology Criteria for Adverse Events (CTCAE) v5.0 determined by the investigator to be related to study procedures (phlebotomy) and occurring during the study period will be recorded. The clinical course of each related event will be followed until resolution, stabilization, or until it has been determined that study participation is not the cause. Adverse events related to a study procedure will be reported to the study sponsor and IRB, in accordance with IRB reporting requirements.

8 Study Administration, Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). These regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

8.2 Data Collection and Management

Identifiable data collected will be kept secure as per site standards, such as storage in a locked office in a locked cabinet to which only the PI has the key or on a password-protected computer within a password protected file, or equivalent.

De-identified data will be centrally recorded in an online database in REDCap Cloud. REDCap Cloud is a 21 CFR Part 11 and HIPPA compliant cloud platform for electronic collection and management of research and clinical trial data. Subjects will only be identified in this database by a subject ID. Access will be password protected and limited to essential study personnel. Sites will maintain a record linking the subject's identity to the subject ID and will retain this record in a secure method as described above.

9 Study Monitoring

Site investigators are expected to ensure that data are collected appropriately. Study data entered in the study database will be reviewed by the study sponsor or designee on a regular basis to ensure data quality and timely data entry.

10 Ethical Considerations

This study is to be conducted in accordance with applicable United States government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or IRB, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

10.1 Risks

Blood draw risks: Risks and discomfort associated with vena-puncture are minor and include swelling, bruising/bleeding at the site, fainting, and, more rarely, the risk of infection at the needle puncture site. These risks are minimized by use of good clinical techniques.

Risk of loss of confidentiality: There is small risk of loss of confidentiality if identifiable data were inadvertently accessed by someone outside the study team. This risk is minimized by the use of secure storage methods.

10.2 Benefits

Subjects are not expected to directly benefit from this study. Knowledge gained from this study may benefit patients with sickle cell disease.

10.3 Risk Benefit Assessment

The procedures in this protocol are of minimal risk and mainly associated with the risk of phlebotomy. These risks are minimized through the implementation of good clinical techniques. The benefit and relevance of the knowledge gained from this study offset the risks associated with participating.

11 Study Finances

11.1 Funding Source

American Society of Hematology Research Collaborative is the sponsor of the study with funding support from the American Society of Hematology.

11.2 Subject Payments

Modest remuneration will be provided to participants in the study to help defray the cost of travel, meals, time, etc. The following represents the projected compensation scheme for each subject; however, payments may be made in installments that accommodate participant scheduling: Subjects will receive $50 per in person visit and $25 per telephone/remote visits for a total of $200-225 for completing all study visits.

12 References

1. Brousse V, Buffet P, Rees D. The spleen and sickle cell disease: the sick(led) spleen. *Br J Haematol.* 2014;166(2):165-176.

2. Panepinto JA, Brandow A, Mucalo L, et al. Coronavirus Disease among Persons with Sickle Cell Disease, United States, March 20-May 21, 2020. *Emerg Infect Dis.* 2020;26(10):2473-2476.

3. Hord J, Windsor B, Koehler M, Blatt J, Janosky J, Mirro J. Diminished antibody response to hepatitis B immunization in children with sickle cell disease. *J Pediatr Hematol Oncol.* 2002;24(7):548-549.

4. ElAlfy MS, Adly AAM, Ebeid FSE, et al. Immunological role of CD4(+)CD28(null) T lymphocytes, natural killer cells, and interferon-gamma in pediatric patients with sickle cell disease: relation to disease severity and response to therapy. *Immunol Res.* 2018;66(4):480-490.

5. Balandya E, Reynolds T, Obaro S, Makani J. Alteration of lymphocyte phenotype and function in sickle cell anemia: Implications for vaccine responses. *Am J Hematol.* 2016;91(9):938-946.

6. Nagant C, Barbezange C, Dedeken L, et al. Alteration of humoral, cellular and cytokine immune response to inactivated influenza vaccine in patients with Sickle Cell Disease. *PloS one.* 2019;14(10):e0223991.

7. Koehl B, Aupiais C, Schinckel N, et al. Tolerance and humoral immune response to the yellow fever vaccine in sickle cell disease children treated with hydroxyurea: a multicentre prospective study. *Journal of travel medicine.* 2021;28(3).

8. Carver CS. You want to measure coping but your protocol's too long: consider the brief COPE. *International Journal of Behvioral Medicine*. 1997; 4(1),92-100.

9. Maybery D, Steer S, Ruepert A, Goodyear M. The Kids Coping Scale. *Stress and Health*. 2009;25:31-40.

10. Flannery DD, Gouma S, Dhudasia MB, et al. SARS-CoV-2 seroprevalence among parturient women in Philadelphia. *Sci Immunol.* 2020;5(49).

11. Vaccines and Related Biological Products Advisory Committee. Vaccines and Related Biological Products Advisory Committee December 17, 2020, meeting: sponsor briefing document. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2020. https://www.fda.gov/media/144452/download

Appendix A: Schedule of Events

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	-30 to 0 days before COVID-19 vaccine (N=52)	2 – 3 days following first/only vaccine (	14 days (±3 days) following first vaccine dose	2 – 3 days following second vaccine**	2 months (±1 week) following first/only vaccine***	6 months (±2 weeks) following first/only vaccine
Informed consent*	X					
Questionnaires	X				X	X
Blood draw	X				X	X
Phone/email survey		X	X	X		

*Informed consent may be obtained prior to Visit 1.
**If the subject received a single-dose vaccine, then Visit 4 will not occur.
*** If second dose of a 2-dose series is administered more than 5 weeks after the 1st dose, Visit 5 should be delayed to occur 3-4 weeks after the 2nd dose is administered. If the 2nd dose is not administered by the initial Visit 5 window, Visit 5 should occur as scheduled.